C-1.12.1

The Deputy Director
Central Intelligence Agency

Executive Registry
77-3194/5

Washington, D.C. 20505

26 March 1977

MEMORANDUM FOR: Executive Secretary, NFIB

SUBJECT: Proposed DCID 9/1 - "Guidelines for Human Subject Research Within the Intelligence Community"

1. Attached is the Agency's summary evaluation of proposed DCID 9/1 and a copy of the guidelines for human subject research which I have approved for use within the CIA. Both were prepared by the Agency's Human Subject Guidelines Working Group and should be useful in preparing a revised Community directive.

2. I urge that particular attention be given to the subject of human research which involves the use of clandestine resources and/or which takes place outside the United States. In addition, the final directive should also reflect the results of the current study of institutional review boards being conducted by the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research.

STAT STAT 3. Any question about the Agency's comments or guidelines should be addressed to [redacted], Office of Research and Development, Directorate of Science and Technology [redacted]

STAT [redacted]
E. H. Knoche

Attachments:
CIA Evaluation of DCID 9/1
CIA Guidelines

([redacted] C-1.12.1)

MEMORANDUM FOR: Secretary, NFIB

SUBJECT: Proposed DCID 9/1 - "Guidelines for Human Subject Research Within the Intelligence Community"

Distribution:

STAT

CIA EVALUATION OF PROPOSED DCID 9/1

Proposed DCID 9/1:

1. Contains errors of fact. The attachment to the proposed DCID, which purports to summarize key elements of the DHEW Human Subject Guidelines, is found to be inaccurate and misleading when compared with the actual DHEW guidelines, 45 CFR 46 (rev. 1 Oct 76).

2. Does not provide interpretation of 45 CFR 46 (rev. 1 Oct 76) where necessary to protect the interests of security or preserve the validity of experimental procedures.

3. Does not incorporate restrictions imposed on the Intelligence Community by E.O. 11905 with regard to drug experimentation.

4. Adopts procedures that go beyond those recommended by DHEW, the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research, and E.O. 11905.

5. Does not specifically indicate who is responsible for protecting the rights and welfare of human subjects at risk. Note that DHEW policy (§ 46.102 (a), (b)(2), (e)) places primary responsibility on the institution which receives or is accountable for the funds awarded in support of the research activity.

6. Does not protect intelligence sources and methods. It raises unnecessarily the question of project sponsorship and does not consider the use of clandestine resources.

26 March 1977

MEMORANDUM FOR: Deputy Director for Administration
Deputy Director for Operations
Deputy Director for Intelligence
Deputy Director for Science and Technology
General Counsel
Inspector General
Legislative Counsel
Comptroller

SUBJECT: Guidelines for Human Subject Research

Pursuant to Section 102 of the National Security Act of 1947, Executive Order 11905, and National Security Council Intelligence Directives, a policy is hereby established for the protection of human subjects of research activities conducted or funded by the Central Intelligence Agency.

1. Purpose

The purpose of this memorandum is to provide policy guidance to assure that research involving human subjects at risk, conducted or funded by the Central Intelligence Agency, will be in accordance with:

a. ethical concerns for the preservation of human life, rights, and dignity,

b. all applicable statutes, applicable Executive Branch directives, and applicable agency or department regulations, and,

c. the procedures which are established to protect the intelligence sources, methods, or data in research.

2. General Guidance

a. Protection of Research Subjects

(1) The Department of Health, Education and Welfare (DHEW) Regulations (45 CFR 46 - Protection of Human Subjects, revised 1 October 1976), portions of which include recommendations of the National Commission for the Pro-

tection of Human Subjects of Biomedical and Behavioral Research, shall represent the minimum acceptable standards governing the treatment of human research subjects. (Attachment)

(2) Section 46.103(C)(5) of the DHEW Regulations provides that a basic element that contributes to informed consent is the information given in response to an individual's inquiries about research procedures. However, this is not to be interpreted to require any answers or information inconsistent with either experimental design or security considerations.

(3) To receive funding from the CIA, an approved assurance must be obtained from the DHEW/Office of Protection from Research Risks, by the organization proposing to conduct the research effort.

(4) The organization conducting the research assumes responsibility for: (a) compliance with 45 CFR 46 (rev. 1 October 1976), all applicable statutes, and those Executive Branch directives and agency or department regulations supplied by the CIA; and (b) providing adequate protection for the rights and welfare of human subjects at risk.

(5) Experimentation with drugs on human subjects will, in addition, be subject to restrictions imposed by E.O. 11905, section 5(d).

(6) If, in the judgment of the CIA, an institution has failed materially to comply with the terms of this policy statement with respect to a particular contract or grant, the CIA may require that said contract or grant be terminated in the manner prescribed in applicable contract or procurement regulations.

b. Protection of Intelligence Sources, Methods, or Data

Only those individuals possessing appropriate security clearances and signing secrecy non-disclosure agreements may be provided with classified information appropriate to the research study.

3. Applicability

a. Data collected in the normal course or as a by-product of approved administrative or operational actions, and therefore not subject to the policy guidelines stated herein, may subsequently be made available for use in formal research projects if adequate safeguards are provided to preserve subject confidentiality.

b. The procedures described in the preceding paragraphs, except paragraph 2a(5), apply to all human subject research, involving U.S. persons at risk, funded or conducted by the Central Intelligence Agency.

STAT [redacted]

E. H. Knoche
Deputy Director of Central Intelligence

Attachment

Attachment I

CODE OF FEDERAL REGULATIONS

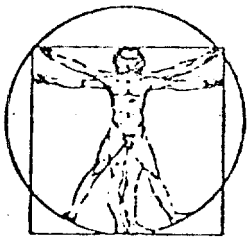
TITLE 45

PUBLIC WELFARE

DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE

REVISED AS OF NOVEMBER 6, 1975

CORRECT TO 1 OCT '76



PART 46—PROTECTION OF HUMAN SUBJECTS

Subpart A

Sec.

46.101 Applicability.
46.102 Policy.
46.103 Definitions.
46.104 Submission of assurances.
46.105 Types of assurances.
46.106 Minimum requirements for general assurances.
46.107 Minimum requirements for special assurances.
46.108 Evaluation and disposition of assurances.

(Cont'd)

Sec.
46.109 Obligation to obtain informed consent; prohibition of exculpatory clauses.
46.110 Documentation of informed consent.
46.111 Submission and certification of applications and proposals, general assurances.
46.112 Submission and certification of applications and proposals, special assurances.
46.113 Applications and proposals lacking definite plans for involvement of human subjects.
46.114 Applications and proposals submitted with the intent of not involving human subjects.
46.115 Evaluation and disposition of applications and proposals.
46.116 Cooperative activities.
46.117 Investigational new drug 30-day delay requirement.
46.118 Institution's executive responsibility.
46.119 Institution's records; confidentiality.
46.120 Reports.
46.121 Early termination of awards; evaluation of subsequent applications and proposals.
46.122 Conditions.

Subpart B—Additional Protections Pertaining to Research, Development, and Related Activities Involving Fetuses, Pregnant Women, and Human In Vitro Fertilization

46.201 Applicability.
46.202 Purpose.
46.203 Definitions.
46.204 Ethical Advisory Boards.
46.205 Additional duties of the Institutional Review Boards in connection with activities involving fetuses, pregnant women, or human in vitro fertilization.
46.206 General limitations.
46.207 Activities directed toward pregnant women as subjects.
46.208 Activities directed toward fetuses in utero as subjects.
46.209 Activities directed toward fetuses ex utero, including nonviable fetuses, as subjects.
46.210 Activities involving the dead fetus, fetal material, or the placenta.
46.211 Modification or waiver of specific requirements.

Subpart C—General Provisions

46.301 Activities conducted by Department employees.

AUTHORITY: 5 U.S.C. 301; sec. 474(a), 88 Stat. 352 (42 U.S.C. 2891-3(a)) unless otherwise noted.

Subpart A

SOURCE: 40 FR 11854, Mar. 13, 1975. Redesignated at 40 FR 33528, Aug. 8, 1975.

§ 46.101 Applicability.

(a) The regulations in this part are applicable to all Department of Health, Education, and Welfare grants and contracts supporting research, development, and related activities in which human subjects are involved.

(b) The Secretary may, from time to time, determine in advance whether specific programs, methods, or procedures to which this part is applicable place subjects at risk, as defined in §46.103(b). Such determinations will be published as notices in the FEDERAL REGISTER and will be included in an appendix to this part.

§ 46.102 Policy.

(a) Safeguarding the rights and welfare of subjects at risk in activities supported under grants and contracts from DHEW is primarily the responsibility of the institution which receives or is accountable to DHEW for the funds awarded for the support of the activity. In order to provide for the adequate discharge of this institutional responsibility, it is the policy of DHEW that no activity involving human subjects to be supported by DHEW grants or contracts shall be undertaken unless an Institutional Review Board has reviewed and approved such activity, and the institution has submitted to DHEW a certification of such review and approval, in accordance with the requirements of this part.

(b) This review shall determine whether these subjects will be placed at risk, and, if risk is involved, whether:

(1) The risks to the subject are so outweighed by the sum of the benefit to the subject and the importance of the knowledge to be gained as to warrant a decision to allow the subject to accept these risks;

(2) The rights and welfare of any such subjects will be adequately protected; and

(3) Legally effective informed consent will be obtained by adequate and appropriate methods in accordance with the provisions of this part.

(c) Unless the activity is covered by Subpart B of this Part, if it involves as subjects women who could become pregnant, the Board shall also determine as part of its review that adequate steps will be taken in the conduct of the activity to avoid involvement of women who are in fact pregnant, when such activity would involve risk to a fetus.

(d) Where the Board finds risk is involved under paragraph (b) of this section, it shall review the conduct of the

activity at timely intervals.

(e) No grant or contract involving human subjects at risk shall be made to an individual unless he is affiliated with or sponsored by an institution which can and does assume responsibility for the subjects involved.

[40 FR 11854, Mar. 13, 1975. Redesignated and amended at 40 FR 33528, Aug. 8, 1975]

§ 46.103 Definitions.

(a) "Institution" means any public or private institution or agency (including Federal, State, and local government agencies).

(b) "Subject at risk" means any individual who may be exposed to the possibility of injury, including physical, psychological, or social injury, as a consequence of participation as a subject in any research, development, or related activity which departs from the application of those established and accepted methods necessary to meet his needs, or which increases the ordinary risks of daily life, including the recognized risks inherent in a chosen occupation or field of service.

(c) "Informed consent" means the knowing consent of an individual or his legally authorized representative, so situated as to be able to exercise free power of choice without undue inducement or any element of force, fraud, deceit, duress, or other form of constraint or coercion. The basic elements of information necessary to such consent include:

(1) A fair explanation of the procedures to be followed, and their purposes, including identification of any procedures which are experimental;

(2) A description of any attendant discomforts and risks reasonably to be expected;

(3) A description of any benefits reasonably to be expected;

(4) A disclosure of any appropriate alternative procedures that might be advantageous for the subject;

(5) An offer to answer any inquiries concerning the procedures; and

(6) An instruction that the person is free to withdraw his consent and to discontinue participation in the project or activity at any time without prejudice to the subject.

(d) "Secretary" means the Secretary of Health, Education, and Welfare or any other officer or employee of the Department of Health, Education, and Welfare to whom authority has been delegated.

(e) "DHEW" means the Department of Health, Education, and Welfare.

(f) "Approved assurance" means a document that fulfills the requirements of this part and is approved by the Secretary.

(g) "Certification" means the official institutional notification to DHEW in accordance with the requirements of this part that a project or activity involving human subjects at risk has been reviewed and approved by the institution in accordance with the "approved assurance" on file at DHEW.

(h) "Legally authorized representative" means an individual or judicial or other body authorized under applicable law to consent on behalf of a prospective subject to such subject's participation in the particular activity or procedure.

§ 46.104 Submission of assurances.

(a) Recipients or prospective recipients of DHEW support under a grant or contract involving subjects at risk shall provide written assurance acceptable to DHEW that they will comply with DHEW policy as set forth in this part. Each assurance shall embody a statement of compliance with DHEW requirements for initial and continuing Institutional Review Board review of the supported activities; a set of implementing guidelines, including identification of the Board and a description of its review procedures; or, in the case of special assurances concerned with single activities or projects, a report of initial findings of the Board and of its proposed continuing review procedures.

(b) Such assurance shall be executed by an individual authorized to act for the institution and to assume on behalf of the institution the obligations imposed by this part, and shall be filed in such form and manner as the Secretary may require.

§ 46.105 Types of assurances.

(a) *General assurances.* A general assurance describes the review and implementation procedures applicable to all DHEW-supported activities conducted by an institution regardless of the number, location, or types of its components or field activities. General assurances will be required from institutions having a significant number of concurrent DHEW-supported projects or activities involving human subjects.

(b) *Special assurances.* A special assurance will, as a rule, describe those

review and implementation procedures applicable to a single activity or project. A special assurance will not be solicited or accepted from an institution which has on file with DHEW an approved general assurance.

§ 46.106 Minimum requirements for general assurances.

General assurances shall be submitted in such form and manner as the Secretary may require. The institution must include, as part of its general assurance, implementing guidelines that specifically provide for:

(a) A statement of principles which will govern the institution in the discharge of its responsibilities for protecting the rights and welfare of subjects. This may include appropriate existing codes or declarations, or statements formulated by the institution itself. It is to be understood that no such principles supersede DHEW policy or applicable law.

(b) An Institutional Review Board or Board structure which will conduct initial and continuing reviews in accordance with the policy outlined in §46.107 Such Board structure or Board shall meet the following requirements:

(1) The Board must be composed of not less than five persons with varying backgrounds to assure complete and adequate review of activities commonly conducted by the institution. The Board must be sufficiently qualified through the maturity, experience, and expertise of its members and diversity of its membership to insure respect for its advice and counsel for safeguarding the rights and welfare of human subjects. In addition to possessing the professional competence necessary to review specific activities, the Board must be able to ascertain the acceptability of applications and proposals in terms of institutional commitments and regulations, applicable law, standards of professional conduct and practice, and community attitudes. The Board must therefore include persons whose concerns are in these areas.

(2) The Board members shall be identified to DHEW by name; earned degrees, if any; position or occupation; representative capacity; and by other pertinent indications of experience such as board certification, licenses, etc., sufficient to describe each member's chief anticipated contributions to Board deliberations. Any employment or other relationship between each member and the institution shall be identified, i.e., full-time employee, part-time employee, member of governing panel or board, paid consultant, unpaid consultant. Changes in Board membership shall be reported to DHEW in such form and at such times as the Secretary may require.

(3) No member of a Board shall be involved in either the initial or continuing review of an activity in which he has a conflicting interest, except to provide information requested by the Board.

(4) No Board shall consist entirely of persons who are officers, employees, or agents, of, or are otherwise associated with the institution, apart from their membership on the Board.

(5) No Board shall consist entirely of members of a single professional group.

(6) The quorum of the Board shall be defined, but may in no event be less than a majority of the total membership duly convened to carry out the Board's responsibilities under the terms of the assurance.

(c) Procedures which the institution will follow in its initial and continuing review of applications, proposals, and activities.

(d) Procedures which the Board will follow (1) to provide advice and counsel to activity directors and investigators with regard to the Board's actions, (2) to insure prompt reporting to the Board of proposed changes in an activity and of unanticipated problems involving risk to subjects or others, and (3) to insure that any such problems, including adverse reactions to biologicals, drugs, radioisotope labelled drugs, or to medical devices, are promptly reported to DHEW.

(e) Procedures which the institution will follow to maintain an active and effective Board and to implement its recommendations.

§ 46.107 Minimum requirements for special assurances.

Special assurances shall be submitted in such form and manner as the Secretary may require. An acceptable special assurance shall:

(a) Identify the specific grant or contract involved by its full title; and by the name of the activity or project director, principal investigator, fellow, or other person immediately responsible for the conduct of the activity.

(b) Include a statement, executed by an appropriate institutional official, in-

dicating that the institution has established an Institutional Review Board satisfying the requirements of §46.106(b)

(c) Describe the makeup of the Board and the training, experience, and background of its members, as required by §46.106(b)(2).

(d) Describe in general terms the risks to subjects that the Board recognizes as inherent in the activity, and justify its decision that these risks are so outweighed by the sum of the benefit to the subject and the importance of the knowledge to be gained as to warrant the Board's decision to permit the subject to accept these risks.

(e) Describe the informed consent procedures to be used and attach documentation as required by §46.110

(f) Describe procedures which the Board will follow to insure prompt reporting to the Board of proposed changes in the activity and of any unanticipated problems, involving risks to subjects or others and to insure that any such problems, including adverse reactions to biologicals, drugs, radioisotope labelled drugs, or to medical devices are promptly reported to DHEW.

(g) Indicate at what time intervals the Board will meet to provide for continuing review. Such review must occur no less than annually.

(h) Be signed by the individual members of the Board and be endorsed by an appropriate institutional official.

§ 46.108 Evaluation and disposition of assurances.

(a) All assurances submitted in accordance with §46.106 and §46.107 shall be evaluated by the Secretary through such officers and employees of DHEW and such experts or consultants engaged for this purpose as he determines to be appropriate. The Secretary's evaluation shall take into consideration, among other pertinent factors, the adequacy of the proposed Institutional Review Board in the light of the anticipated scope of the applicant institution's activities and the types of subject populations likely to be involved, the appropriateness of the proposed initial and continuing review procedures in the light of the probable risks, and the size and complexity of the institution.

(b) On the basis of his evaluation of an assurance pursuant to paragraph (a) of this section, the Secretary shall (1) approve, (2) enter into negotiations to develop a more satisfactory assurance, or (3) disapprove. With respect to approved assurances, the Secretary may determine the period during which any particular assurance or class of assurances shall remain effective or otherwise condition or restrict his approval. With respect to negotiations, the Secretary may, pending completion of negotiations for a general assurance, require an institution otherwise eligible for such an assurance, to submit special assurances.

§ 46.109 Obligation to obtain informed consent; prohibition of exculpatory clauses.

Any institution proposing to place any subject at risk is obligated to obtain and document legally effective informed consent. No such informed consent, oral or written, obtained under an assurance provided pursuant to this part shall include any exculpatory language through which the subject is made to waive, or to appear to waive, any of his legal rights, including any release of the institution or its agents from liability for negligence.

§ 46.110 Documentation of informed consent.

The actual procedure utilized in obtaining legally effective informed consent and the basis for Institutional Review Board determinations that the procedures are adequate and appropriate shall be fully documented. The documentation of consent will employ one of the following three forms:

(a) Provision of a written consent document embodying all of the basic elements of informed consent. This may be read to the subject or to his legally authorized representative, but in any event he or his legally authorized representative must be given adequate opportunity to read it. This document is to be signed by the subject or his legally authorized representative. Sample copies of the consent form as approved by the Board are to be retained in its records.

(b) Provision of a "short form" written consent document indicating that the basic elements of informed consent have been presented orally to the subject or his legally authorized representative. Written summaries of what is to be said to the patient are to be approved by the Board. The short form is to be signed by the subject or his legally authorized representative and by an auditor witness to the oral presentation and to the subject's signature. A copy of the approved

summary, annotated to show any additions, is to be signed by the persons officially obtaining the consent and by the auditor witness. Sample copies of the consent form and of the summaries as approved by the Board are to be retained in its records.

(c) Modification of either of the primary procedures outlined in paragraphs (a) and (b) of this section. Granting of permission to use modified procedures imposes additional responsibility upon the Board and the institution to establish: (1) That the risk to any subject is minimal, (2) that use of either of the primary procedures for obtaining informed consent would surely invalidate objectives of considerable immediate importance, and (3) that any reasonable alternative means for attaining these objectives would be less advantageous to the subjects. The Board's reasons for permitting the use of modified procedures must be individually and specifically documented in the minutes and in reports of Board actions to the files of the institution. All such modifications should be regularly reconsidered as a function of continuing review and as required for annual review, with documentation of reaffirmation, revision, or discontinuation, as appropriate.

§ 46.111 Submission and certification of applications and proposals, general assurances.

(a) *Timely review.* Any institution having an approved general assurance shall indicate in each application or proposal for support of activities covered by this part (or in a separate document submitted with such application or proposal) that it has on file with DHEW such an assurance. In addition, unless the Secretary otherwise provides, each such application or proposal must be given review and, when found to involve subjects at risk, approval, prior to submission to DHEW. In the event the Secretary provides for the performance of institutional review of an application or proposal after its submission to DHEW, processing of such application or proposal by DHEW will under no circumstances be completed until such institutional review and approval has been certified. Except where the institution determines that human subjects are not involved, the application or proposal should be appropriately certified in the spaces provided on forms, or one of the following certifications, as appropriate, should be typed on the lower or right hand margin of the page bearing the name of an official authorized to sign or execute applications or proposals for the institution.

Human Subjects: Reviewed, Not at Risk.

(Date)

Human Subjects: Reviewed, At Risk, Approved

(Date)

(b) *Applications and proposals not certified.* Applications and proposals not properly certified, or submitted as not involving human subjects and found by the operating agency to involve human subjects, will be returned to the institution concerned.

§ 46.112 Submission and certification of applications and proposals, special assurances.

(a) Except as provided in paragraph (b) of this section, institutions not having an approved general assurance shall submit in or with each application or proposal for support of activities covered by this part a separate special assurance and certification of its review and approval.

(b) If the Secretary so provides, the assurance which must be submitted in or with the application or proposal under paragraph (a) of this section need satisfy only the requirements of §46.107(a) and §46.107(b) Under such circumstances, processing of such application or proposal by DHEW will not be completed until a further assurance satisfying the remaining requirements of §46.107 has been submitted to DHEW.

(c) An assurance and certification prepared in accordance with this part and approved by DHEW shall be considered to have met the requirement for certification for the initial grant or contract period concerned. If the terms of the grant or contract recommend additional support periods, each application or proposal for continuation or renewal of support must satisfy the requirements of this section or §46.111 whichever is applicable at the time of its submission.

§ 46.113 Applications and proposals lacking definite plans for involvement of human subjects.

Certain types of applications or proposals are submitted with the knowledge that subjects are to be involved within

the support period, but definite plans for this involvement would not normally be set forth in the application or proposal. These include such activities as (a) institutional type grants where selection of projects is the responsibility of the institution, (b) training grants where training projects remain to be selected, and (c) research, pilot, or developmental studies in which involvement depends upon such things as the completion of instruments, or of prior animal studies, or upon the purification of compounds. Such applications or proposals shall be reviewed and certified in the same manner as more definitive applications, or proposals. The initial certification indicates institutional approval of the applications or proposals as submitted, and commits the institution to later review of the plans when completed. Such later review and certification to DHEW should be completed prior to the beginning of the budget period during which actual involvement of human subjects is to begin. Review and certification to DHEW must in any event be completed prior to involvement of human subjects.

§ 46.114 Applications and proposals submitted with the intent of not involving human subjects.

If an application or proposal does not anticipate involving or intend to involve human subjects, no certification should be included with the initial submission of the application or proposal. In those instances, however, when later it becomes appropriate to use all or part of awarded funds for one or more activities which will involve subjects, each such activity shall be reviewed and approved in accordance with the assurance of the institution prior to the involvement of subjects. In addition, no such activity shall be undertaken until the institution has submitted to DHEW, (a) A certification that the activity has been reviewed and approved in accordance with this part, and (b) a detailed description of the proposed activity (including any protocol or similar document). Also, where support is provided by project grants or contracts, subjects shall not be involved prior to certification and institutional receipt of DHEW approval and, in the case of contracts, prior to negotiation and approval of an amended contract description of work.

§ 46.115 Evaluation and disposition of applications and proposals.

(a) Notwithstanding any prior review, approval, and certification by the institution all applications or proposals involving human subjects at risk submitted to DHEW shall be evaluated by the Secretary for compliance with this part through such officers and employees of the Department and such experts or consultants engaged for this purpose as he determines to be appropriate. This evaluation may take into account, among other pertinent factors, the apparent risks to the subjects, the adequacy of protection against these risks, the potential benefits of the activity to the subjects and to others, and the importance of the knowledge to be gained.

(b) Disposition. On the basis of his evaluation of an application or proposal pursuant to paragraph (a) of this section and subject to such approval or recommendation by or consultation with appropriate councils, committees, or other bodies as may be required by law, the Secretary shall (1) approve, (2) defer for further evaluation, or (3) disapprove support of the proposed activity in whole or in part. With respect to any approved grant or contract, the Secretary may impose conditions, including restrictions on the use of certain procedures, or certain subject groups, or requiring use of specified safeguards or informed consent procedures when in his judgment such conditions are necessary for the protection of human subjects.

§ 46.116 Cooperative activities.

Cooperative activities are those which involve institutions in addition to the grantee or prime contractor (such as a contractor under a grantee or a subcontractor under a prime contractor). If, in such instances, the grantee or prime contractor obtains access to all or some of the subjects involved through one or more cooperating institutions, the basic DHEW policy applies and the grantee or prime contractor remains responsible for safeguarding the rights and welfare of the subjects.

(a) *Institution with approved general assurance.* Initial and continuing review by the institution may be carried out by one or a combination of procedures:

(1) Cooperating institution with approved general assurance. When the cooperating institution has on file with

DHEW an approved general assurance, the grantee or contractor may, in addition to its own review, request the cooperating institution to conduct an independent review and to report its recommendations on those aspects of the activity that concern individuals for whom the cooperating institution has responsibility under its own assurance to the grantee's or contractor's Institutional Review Board. The grantee or contractor may, at its discretion, concur with or further restrict the recommendations of the cooperating institution. It is the responsibility of the grantee or contractor to maintain communication with the Boards of the cooperating institution. However, the cooperating institution shall promptly notify the grantee or contracting institution whenever the cooperating institution finds the conduct of the project or activity within its purview unsatisfactory.

(2) Cooperating institution with no approved general assurance. When the cooperating institution does not have an approved general assurance on file with DHEW, the DHEW may require the submission of a general or special assurance which, if approved, will permit the grantee or contractor to follow the procedure outlined in the preceding subparagraph.

(3) Interinstitutional joint review. The grantee or contracting institution may wish to develop an agreement with cooperating institutions to provide for an Institutional Review Board with representatives from cooperating institutions. Representatives of cooperating institutions may be appointed as ad hoc members of the grantee or contracting institution's existing Institutional Review Board or, if cooperation is on a frequent or continuing basis as between a medical school and a group of affiliated hospitals, appointments for extended periods may be made. All such cooperative arrangements must be approved by DHEW as part of a general assurance, or as an amendment to a general assurance.

(b) *Institutions with special assurances.* While responsibility for initial and continuing review necessarily lies with the grantee or contracting institution, DHEW may also require approved assurances from those cooperating institutions having immediate responsibility for subjects.

If the cooperating institution has on file with DHEW an approved general assurance, the grantee or contractor shall request the cooperating institution to conduct its own independent review of those aspects of the project or activity which will involve human subjects for which it has responsibility. Such a request shall be in writing and should provide for direct notification of the grantee's or contractor's Institutional Review Board in the event that the cooperating institution's Board finds the conduct of the activity to be unsatisfactory. If the cooperating institution does not have an approved general assurance on file with DHEW, it must submit to DHEW a general or special assurance which is determined by DHEW to comply with the provisions of this part.

§ 46.117 Investigational new drug 30-day delay requirement.

Where an institution is required to prepare or to submit a certification under §§ 46.111, 46.112, 46.113 or 46.114 and the application or proposal involves an investigational new drug within the meaning of The Food, Drug, and Cosmetic Act, the drug shall be identified in the certification together with a statement that the 30-day delay required by 21 CFR 312.1(a)(2) has elapsed and the Food and Drug Administration has not, prior to expiration of such 30-day interval, requested that the sponsor continue to withhold or to restrict use of the drug in human subjects; or that the Food and Drug Administration has waived the 30-day delay requirement: *Provided, however,* That in those cases in which the 30-day delay interval has neither expired nor been waived, a statement shall be forwarded to DHEW upon such expiration or upon receipt of a waiver. No certification shall be considered acceptable until such statement has been received.

§ 46.118—Institution's executive responsibility.

Specific executive functions to be conducted by the institution include policy development and promulgation and continuing indoctrination of personnel. Appropriate administrative assistance and support shall be provided for the Board's functions. Implementation of the Board's recommendations through appropriate administrative action and followup is a condition of DHEW approval of an assurance. Board approvals, favorable actions,

and recommendations are subject to review and to disapproval or further restriction by the institution officials. Board disapprovals, restrictions, or conditions cannot be rescinded or removed except by action of a Board described in the assurance approved by DHEW.

§ 46.119 Institution's records; confidentiality.

(a) Copies of all documents presented or required for initial and continuing review by the Institutional Review Board, such as Board minutes, records of subject's consent, transmittals on actions, instructions, and conditions resulting from Board deliberations addressed to the activity director, are to be retained by the institution, subject to the terms and conditions of grant and contract awards.

(b) Except as otherwise provided by law information in the records or possession of an institution acquired in connection with an activity covered by this part, which information refers to or can be identified with a particular subject, may not be disclosed except:

(1) With the consent of the subject or his legally authorized representative; or

(2) As may be necessary for the Secretary to carry out his responsibilities under this part.

§ 46.120 Reports.

Each institution with an approved assurance shall provide the Secretary with such reports and other information as the Secretary may from time to time prescribe.

§ 46.121 Early termination of awards; evaluation of subsequent applications and proposals.

(a) If, in the judgment of the Secretary an institution has failed materially to comply with the terms of this policy with respect to a particular DHEW grant or contract, he may require that said grant or contract be terminated or suspended in the manner prescribed in applicable grant or procurement regulations.

(b) In evaluating applications or proposals for support of activities covered by this part, the Secretary may take into account, in addition to all other eligibility requirements and program criteria, such factors as: (1) Whether the applicant or offeror has been subject to a termination or suspension under paragraph (a) of this section, (2) whether the applicant or offeror or the person who would direct the scientific and technical aspects of an activity has in the judgment of the Secretary failed materially to discharge his, her, or its responsibility for the protection of the rights and welfare of subjects in his, her, or its care (whether or not DHEW funds were involved), and (3) whether, where past deficiencies have existed in discharging such responsibility, adequate steps have in the judgment of the Secretary been taken to eliminate these deficiencies.

§ 46.122 Conditions.

The Secretary may with respect to any grant or contract or any class of grants or contracts impose additional conditions prior to or at the time of any award when in his judgment such conditions are necessary for the protection of human subjects.

Subpart B—Additional Protections Pertaining to Research, Development, and Related Activities Involving Fetuses, Pregnant Women, and Human In Vitro Fertilization

Source: 40 FR 33528, Aug. 8, 1975, unless otherwise noted.

§ 46.201 Applicability.

(a) The regulations in this subpart are applicable to all Department of Health, Education, and Welfare grants and contracts supporting research, development, and related activities involving: (1) The fetus, (2) pregnant women, and (3) human *in vitro* fertilization.

(b) Nothing in this subpart shall be construed as indicating that compliance with the procedures set forth herein will in any way render inapplicable pertinent State or local laws bearing upon activities covered by this subpart.

(c) The requirements of this subpart are in addition to those imposed under the other subparts of this part.

§ 46.202 Purpose.

It is the purpose of this subpart to provide additional safeguards in reviewing activities to which this subpart is applicable to assure that they conform to appropriate ethical standards and relate to important societal needs.

§ 46.203 Definitions.

As used in this subpart:

(a) "Secretary" means the Secretary of Health, Education, and Welfare and any other officer or employee of the Department of Health, Education, and

Welfare to whom authority has been delegated.

(b) "Pregnancy" encompasses the period of time from confirmation of implantation until expulsion or extraction of the fetus.

(c) "Fetus" means the product of conception from the time of implantation until a determination is made, following expulsion or extraction of the fetus, that it is viable.

(d) "Viable" as it pertains to the fetus means being able, after either spontaneous or induced delivery, to survive (given the benefit of available medical therapy) to the point of independently maintaining heart beat and respiration. The Secretary may from time to time, taking into account medical advances, publish in the FEDERAL REGISTER guidelines to assist in determining whether a fetus is viable for purposes of this subpart. If a fetus is viable after delivery, it is a premature infant.

(e) "Nonviable fetus" means a fetus *ex utero* which, although living, is not viable.

(f) "Dead fetus" means a fetus *ex utero* which exhibits neither heartbeat, spontaneous respiratory activity, spontaneous movement of voluntary muscles, nor pulsation of the umbilical cord (if still attached).

(g) "*In vitro* fertilization" means any fertilization of human ova which occurs outside the body of a female, either through admixture of donor human sperm and ova or by any other means.

§ 46.204 Ethical Advisory Boards.

(a) Two Ethical Advisory Boards shall be established by the Secretary. Members of these Boards shall be so selected that the Boards will be competent to deal with medical, legal, social, ethical, and related issues and may include, for example, research scientists, physicians, psychologists, sociologists, educators, lawyers, and ethicists, as well as representatives of the general public. No board member may be a regular, full-time employee of the Federal Government.

(b) One Board shall be advisory to the Public Health Service and its components. One Board shall be advisory to all other agencies and components within the Department of Health, Education, and Welfare.

(c) At the request of the Secretary, the appropriate Ethical Advisory Board shall render advice consistent with the policies and requirements of this Part as to ethical issues, involving activities covered by this subpart, raised by individual applications or proposals. In addition, upon request by the Secretary, the appropriate Board shall render advice as to classes of applications or proposals and general policies, guidelines, and procedures.

(d) A Board may establish, with the approval of the Secretary, classes of applications or proposals which: (1) Must be submitted to the Board, or (2) need not be submitted to the Board. Where the Board so establishes a class of applications or proposals which must be submitted, no application or proposal within the class may be funded by the Department or any component thereof until the application or proposal has been reviewed by the Board and the Board has rendered advice as to its acceptability from an ethical standpoint.

(e) No application or proposal involving human *in vitro* fertilization may be funded by the Department or any component thereof until the application or proposal has been reviewed by the Ethical Advisory Board and the Board has rendered advice as to its acceptability from an ethical standpoint.

§ 46.205 Additional duties of the Institutional Review Boards in connection with activities involving fetuses, pregnant women, or human in vitro fertilization.

(a) In addition to the responsibilities prescribed for Institutional Review Boards under Subpart A of this part, the applicant's or offeror's Board shall, with respect to activities covered by this subpart, carry out the following additional duties:

(1) Determine that all aspects of the activity meet the requirements of this subpart;

(2) Determine that adequate consideration has been given to the manner in which potential subjects will be selected, and adequate provision has been made by the applicant or offeror for monitoring the actual informed consent process (e.g., through such mechanisms, when appropriate, as participation by the Institutional Review Board or subject advocates in: (i) Overseeing the actual process by which individual consents required by this subpart are secured either by approving induction of each individual into the activity or verifying, perhaps through sampling, that approved procedures for induction of individuals into the activity are being followed, and (ii) monitoring

the progress of the activity and intervening as necessary through such steps as visits to the activity site and continuing evaluation to determine if any unanticipated risks have arisen);

(3) Carry out such other responsibilities as may be assigned by the Secretary.

(b) No award may be issued until the applicant or offeror has certified to the Secretary that the Institutional Review Board has made the determinations required under paragraph (a) of this section and the Secretary has approved these determinations, as provided in § 46.115 of Subpart A of this part.

(c) Applicants or offerors seeking support for activities covered by this subpart must provide for the designation of an Institutional Review Board, subject to approval by the Secretary, where no such Board has been established under Subpart A of this part.

§ 46.206 General limitations.

(a) No activity to which this subpart is applicable may be undertaken unless:

(1) Appropriate studies on animals and nonpregnant individuals have been completed;

(2) Except where the purpose of the activity is to meet the health needs of the mother or the particular fetus, the risk to the fetus is minimal and, in all cases, is the least possible risk for achieving the objectives of the activity.

(3) Individuals engaged in the activity will have no part in: (i) Any decisions as to the timing, method, and procedures used to terminate the pregnancy, and (ii) determining the viability of the fetus at the termination of the pregnancy; and

(4) No procedural changes which may cause greater than minimal risk to the fetus or the pregnant woman will be introduced into the procedure for terminating the pregnancy solely in the interest of the activity.

(b) No inducements, monetary or otherwise, may be offered to terminate pregnancy for purposes of the activity.

§ 46.207 Activities directed toward pregnant women as subjects.

(a) No pregnant woman may be involved as a subject in an activity covered by this subpart unless: (1) The purpose of the activity is to meet the health needs of the mother and the fetus will be placed at risk only to the minimum extent necessary to meet such needs, or (2) the risk to the fetus is minimal.

(b) An activity permitted under paragraph (a) of this section may be conducted only if the mother and father are legally competent and have given their informed consent after having been fully informed regarding possible impact on the fetus, except that the father's informed consent need not be secured if: (1) The purpose of the activity is to meet the health needs of the mother; (2) his identity or whereabouts cannot reasonably be ascertained; (3) he is not reasonably available; or (4) the pregnancy resulted from rape.

§ 46.208 Activities directed toward fetuses *in utero* as subjects.

(a) No fetus *in utero* may be involved as a subject in any activity covered by this subpart unless: (1) The purpose of the activity is to meet the health needs of the particular fetus and the fetus will be placed at risk only to the minimum extent necessary to meet such needs, or (2) the risk to the fetus imposed by the research is minimal and the purpose of the activity is the development of important biomedical knowledge which cannot be obtained by other means.

(b) An activity permitted under paragraph (a) of this section may be conducted only if the mother and father are legally competent and have given their informed consent, except that the father's consent need not be secured if: (1) His identity or whereabouts cannot reasonably be ascertained, (2) he is not reasonably available, or (3) the pregnancy resulted from rape.

§ 46.209 Activities directed toward fetuses *ex utero*, including nonviable fetuses, as subjects.

(a) No fetus *ex utero* may be involved as a subject in an activity covered by this subpart until it has been ascertained whether the particular fetus is viable, unless: (1) There will be no added risk to the fetus resulting from the activity, and (2) the purpose of the activity is the development of important biomedical knowledge which cannot be obtained by other means.

(b) No nonviable fetus may be involved as a subject in an activity covered

by this subpart unless: (1) Vital functions of the fetus will not be artificially maintained except where the purpose of the activity is to develop new methods for enabling fetuses to survive to the point of viability, (2) experimental activities which of themselves would terminate the heartbeat or respiration of the fetus will not be employed, and (3) the purpose of the activity is the development of important biomedical knowledge which cannot be obtained by other means.

(c) In the event the fetus *ex utero* is found to be viable, it may be included as a subject in the activity only to the extent permitted by and in accordance with the requirements of other subparts of this part.

(d) An activity permitted under paragraph (a) or (b) of this section may be conducted only if the mother and father are legally competent and have given their informed consent, except that the father's informed consent need not be secured if: (1) his identity or whereabouts cannot reasonably be ascertained, (2) he is not reasonably available, or (3) the pregnancy resulted from rape.

§ 46.210 Activities involving the dead fetus, fetal material, or the placenta.

Activities involving the dead fetus, mascerated fetal material, or cells, tissue, or organs excised from a dead fetus shall be conducted only in accordance with any applicable State or local laws regarding such activities.

§ 46.211 Modification or waiver of specific requirements.

Upon the request of an applicant or offeror (with the approval of its Institutional Review Board), the Secretary may modify or waive specific requirements of this subpart, with the approval of the Ethical Advisory Board after such opportunity for public comment as the Ethical Advisory Board considers appropriate in the particular instance. In making such decisions, the Secretary will consider whether the risks to the subject are so outweighed by the sum of the benefit to the subject and the importance of the knowledge to be gained as to warrant such modification or waiver and that such benefits cannot be gained except through a modification or waiver. Any such modifications or waivers will be published as notices in the FEDERAL REGISTER.

Subpart C—General Provisions

§ 46.301 Activities conducted by Department employees.

The regulations of this part are applicable as well to all research, development, and related activities conducted by employees of the Department of Health, Education, and Welfare, except that each Principal Operating Component head may adopt such non-substantive procedural modifications as may be appropriate from an administrative standpoint.

[40 FR 33530, Aug. 8, 1975]